III. REMARKS

Reconsideration of this application, in view of the changes made and arguments presented herein, is respectfully requested.

A. Status of the Claims

Claims 1-8 and 10-20 are pending. Claims 1, 10, 17 and 20 have been amended without prejudice to more particularly point out and distinctly claim the invention. Claim 16 has been amended without prejudice to correct a typographical error. The subject matter of claim 9 has been incorporated into claim 1, therefore claim 9 has been cancelled without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

B. Examiner's Comments Regarding Information Disclosure Statement

In the Office Action mailed October 13, 2006, the Examiner stated that the listing of references in the specification is not a proper information disclosure statement. In response, submitted herewith is an Information Disclosure Statement in compliance with 37 C.F.R. § 1.98(b) and M.P.E.P. § 609.04(a), a Form PTO-1449, references cited thereon and the $180.00 requisite fee for submission of an Information Disclosure Statement under 37 C.F.R. 1.17(p).

C. Examiner's Comments Regarding the Oath/Declaration

In the Office Action, the Examiner stated that the oath or declaration is defective because it does not identify the citizenship of each inventor. In response, submitted herewith is a Declaration/Power of Attorney in compliance with 37 C.F.R. § 1.67(a) and M.P.E.P. §§ 602.01 and 602.02 and the required $130.00 surcharge for late filing of the declaration under 37 C.F.R. 1.16(f).

D. Examiner's Comments Regarding the Specification

In the Office Action, the Examiner objected to the specification for failing to provide antecedent basis for "first specific viscosity" and "second specific viscosity" as recited in claims 1, 9-12 and 17. The Examiner also stated that there is a lack of support for the viscosity ranges recited in claims 9-11. The Examiner further stated that there is a lack of support for "sonication" as recited in claim 15. For each of these objections, the Examiner stated that the applicant may amend the specification to bring the terms into the disclosure without the introduction of new matter. In response to this objection, the specification has been amended in this Response by adding new paragraphs [0029.1] through [0029.17]. Support for this amendment can be found in originally filed claims 1-20. Therefore, it is respectfully submitted that no new matter has been added by virtue of this amendment.

E. 35 U.S.C. §112 Rejections

In the Office Action, the Examiner rejected claims 9-11 under 35 U.S.C. §112, first paragraph, for lacking enablement. The Examiner took the position that while the specification is enabling for specific inherent viscosities for PLGA in Examples 12, 13, 15-18, 20, 21 and 23, the specification does not reasonably provide enablement for specific viscosity ranges recited in claims 9-11. The Examiner also took the position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants initially note that the ranges of PLGA's from claim 9 have been incorporated into claim 1 and claim 20. Claim 9 has been cancelled. Claim 10 has been amended to depend from claim 1 rather than claim 9. Therefore the ranges of PLGA viscosity at issue are recited in claims 1, 10, 11 and 20.

The primary issue the Examiner raised in the Office Action is that the following PLGA specific viscosity ranges are not enabled:

- between about 0.01 and about 0.31 dL/g and between about 0.40 and 0.88 dL/g;

- between about 0.12 and about 0.20 dL/g and between about 0.48 and 0.80 dL/g; and

- between about 0.14 and about 0.18 dL/g and between about 0.56 and 0.72 dL/g.

(i) <u>The Examples Provide PLGA's within the Claimed Ranges</u>

Applicants respectfully submit that Examples 13, 15, 16, 17, 18, 20 and 21 disclose preparing microspheres according to the invention using the following two PLGA specific viscosities: 0.16 dL/g and 0.64dL/g. Additionally, Example 23 discloses preparing microspheres according to the invention using the following two PLGA specific viscosities: 0.20 dL/g and 0.66 dL/g.

As stated in MPEP §2164.08:

The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

As to the first stage of the inquiry, Applicants have indeed provided an example of a PLGA that falls within each of the ranges of the first and second PLGA viscosities set forth above.

(ii) <u>The PLGA's in Question are Commercially Available</u>

As to the second stage of the inquiry, the specification itself alludes to a commercial source of standard PLGA products available from BPI (Birmingham Polymers, Inc., which is a subsidiary of Southern BioSystems, Inc., which is a wholly owned subsidiary of Durect Corporation). The BPI materials were used in the Examples.

Applicants submit information from BPI's website uncovered from an initial internet search as **Exhibit A** listing various inherent viscosities of PLGA that it sells. The table entitled "Standard Products" lists PLGA products having the following viscosities: 0.15-0.25 dL/g, 0.26-0.54 dL/g, 0.55-0.75 dL/g, 0.76-0.94 dL/g and 0.95-1.20 dL/g.

Applicants further submit information from BPI's website as **Exhibit B**, stating that in addition to "Standard Products", BPI also makes custom polymers with specific characteristics. Therefore, one of skill would appreciate that PLGA's having specific viscosities within the recited ranges are also commercially available from BPI.

As stated in MPEP§2164.01(b):

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available.

In this case, as demonstrated above, the PLGA's are indeed available.

Applicants further submit an entry from BPI's website as **Exhibit C**, which shows graphical representations of various PLGA polymers where molecular weight in Daltons is plotted against inherent viscosity in dL/g. As one of skill would clearly appreciate, the inherent viscosity increases as the molecular weight of the polymer increases. Therefore one of skill in the art would be able to obtain a higher viscosity PLGA with a higher molecular weight and conversely, a lower viscosity PLGA with a lower molecular weight.

Finally, Applicants submit information from BPI's website as **Exhibit D** describing PLGA commercial applications including controlled release biodegradable microspheres.

Thus, contrary to the Examiner's position, if one of ordinary skill in the art wishes to utilize a PLGA having a particular viscosity within the claimed ranges, there is no undue experimentation involved at all. In fact, there is no experimentation needed. These materials in and of themselves are commercially available, and can even be custom prepared! Accordingly, in order to prepare microspheres from PLGA according to the claimed ranges, one of skill need only contact a commercial source such as BPI and obtain the desired PLGA components, then follow the disclosure of the present specification to prepare and recover the microspheres.

The Examiner took the position that in view of the lack of guidance, working examples, breadth of claims, the level of skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation to make and/or use the invention as claimed. It is respectfully submitted that the guidance provided in the specification enables one of ordinary skill in the art to obtain PLGA's of the desired viscosity and manufacture the microspheres. The level of skill required is low, because one can buy these materials pre-made. The state of the art as demonstrated by the appended Exhibits is such that there is no undue experimentation needed. One only needs to obtain the materials and follow the procedures detailed in the specification. One of ordinary skill in the art could readily obtain commercially available PLGA having a viscosity across the claimed range, prepare and recover the microspheres in connection with the claimed invention.

Accordingly, it is respectfully submitted that the Examiners rejection under 35 U.S.C. § 112, first paragraph of claims 9-11 (as it applies to the claims as amended) has been overcome and should be withdrawn.

F. <u>35 U.S.C. §103 Rejections</u>

The Examiner rejected claims 1-20 under 35 U.S.C. § 103(a) as being obvious over United States Patent No. 5,000,886 to Lawter et al., ("Lawter"), in view of United States Patent No. 6,716,449 to Oshlack et al., ("Oshlack") or Japan Patent Application No. JP 403103732A to Hille et al., ("Hille").

(i) Lawter does not combine 2 PLGA's into one formulation

Even, assuming arguendo, that one could combine the microspheres of Examples 4 and 5 of Lawter, it is respectfully submitted that one would still not arrive at the claimed invention. Each of the PLGA's relied upon by the Examiner in Lawter for this rejection are separately found in completed formulations. Therefore, at best, a combination would result in a combination of populations of each set of microspheres. However, nowhere does Lawter even suggest combining final products made in separate examples or different PLGA's into one formulation.

Moreover, Lawter mentions buprenorphine in a long list of active agents. Nothing in Lawter suggests mixing buprenorphine and two PLGA's of different specific viscosities as now claimed. In fact, Lawter teaches away from the claimed invention by describing the use of only one PLGA having one viscosity, and not a mixture of different materials, in its disclosure. It is respectfully submitted that there is no basis to assert that Lawter hints or suggests that microcapsules having buprenorphine as the active agent should utilize any particular PLGA viscosity, let alone the combination of PLGA's presently claimed. Certainly, there is no general discussion in Lawter of any preferred PLGA's having preferred viscosities; and the examples in Lawter upon which the Examiner relies are directed to completely different active agents having completely different physical/chemical properties.

In this regard, the Examiner is reminded of her position taken at Page 5, second paragraph of the Office Action dated October 13, 2006. Therein, the Examiner states that "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity" (citing *In re Fisher*). Applicants agree, to the extent that the unpredictable nature of the pharmaceutical art does not allow one to pick and choose elements in Lawter to arrive at the presently claimed invention without the impermissible benefit of hindsight. Certainly, Lawter does not provide any motivation whatsoever to pick buprenorphine out of a long list of possible actives, and then further pick two separately considered PLGA's, and then admix them together, to arrive at the

claimed invention. The Examiner's position that "a third composition that contains PLGA having different viscosities and containing buprenorphine is rendered obvious with expectation of success that the compositions can be successfully formulated" (Page 7, second complete paragraph of the Office Action) flies in the face of the Examiner's own admission of the unpredictable nature of the pharmaceutical art and the lack of any suggestion in Lawter to pick and choose and admix two different PLGA viscosity materials to formulate a buprenorphine composition.

It is respectfully submitted that Lawter, taken alone or in combination with either the teachings of Oshlack or the teachings of Hille does not teach all of the elements of the presently claimed invention.

Oshlack does not provide a basis for overcoming the deficiencies of Lawter regarding the claims. Example 20 of Oshlack describes a prophetic example where controlled release microspheres containing buprenorphine and naltrexone are prepared with PLGA and PVA. The microspheres are then suspended in a suitable media for injection such as water. It is respectfully submitted that Example 20 of Oshlack does not specify a viscosity or molecular weight of PLGA.

Hille also fails to provide a basis for overcoming the deficiencies of Lawter regarding the claims. Hille describes a buprenorphine transdermal patch with an impermeable backing layer and pressure-sensitive adhesive reservoir layer comprising a polymeric material. Hille mentions that PVA, among other materials, may be used as the polymeric material. The impermeable backing layer in Hille is preferably an aluminized foil. The transdermal patch also contains a softening agent and a solvent for the active ingredient.

Accordingly, in view of the above arguments, it is respectfully requested that the Examiner's rejection under 35 U.S.C. § 103(a) of claims 1-20 be withdrawn.

IV. Conclusion

In view of the actions taken, it is respectfully submitted that the present application is now in condition for allowance. An early and favorable action on the merits is earnestly solicited. According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview will advance the prosecution of this application. A request for a three-month extension of time to reply to the Office Action along with the requisite fee is enclosed.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Clifford M. Davidson, Esq.
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

EXHIBIT A

At DURECT, our commitment to quality includes a thorough analysis of each lot of polymer. Polymer lots are tested before shipment, and each lot of medical grade polymer is supplied with a Certificate of Analysis (COA). Analyses include identification by 1H-NMR, inherent viscosity (IV), monomer ratio and residual monomer levels by 1H-NMR, residual Sn+2 (from catalyst), bioburden (total aerobes, spores and anaerobes), and pyrogens (LAL). Other analyses can be provided if desired, including FTIR, heavy metals, residual solvents, solubility and cloud point in various solvents, DSC, and other compendial tests. We also have considerable experience using GPC and NMR techniques.

LACTEL Customer Service
Phone: 877-705-8072
Fax: 408-865-1406
E-mail:absorbablescs@durect.com

LACTEL Technical Support
Phone: 205-620-0025
Fax: 205-620-9888
E-mail:
absorbables@durect.com

2685A Pelham Parkway, Pelham AL 35124

EXHIBIT B

The Examiner took the position that Lawter prepares microcapsules of pharmaceutical agents in the presence of halogenated organic solvent such as methylene chloride, phosphate buffer, PLGA having viscosity in one example being 0.65 dL/g and viscosity in another example being 0.29 dL/g and that Lawter contemplates preparing many pharmaceutical agents including buprenorphine with specific emphasis for buprenorphine at column 4, line 37. The Examiner also took the position that while the embodiments exemplified do not contain buprenorphine, any of the drugs listed can be prepared by the process of Lawter. The Examiner concluded that it is "prima facie obvious to combine two compositions each of which is taught by the prior art to be used for the same purpose, in order to form a third composition to be used for the very same purpose . . . [T]he idea of combining them flows logically from their having been individually taught by the prior art", citing In re Kerkhoven, 626 F.2d 846, 850, 205 U.S.P.Q. 1069, 1072 (C.C.P.A. 1980).

The Examiner also took the position that Lawter's buprenorphine formulation does not contain polyvinyl alcohol, and that buprenorphine is known in the art to be formulated with polyvinyl alcohol as is disclosed in Example 20 of Oshlack and as disclosed in the English abstract of Hille. Therefore, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the buprenorphine formulation according to Lawter and include PVA as suggested by Oshlack or Hille.

The Examiner's rejection is respectfully traversed. Applicants respectfully submit that Lawter does not hint or suggest a process for preparing a pharmaceutical formulation for extended release of buprenorphine from microspheres made by admixing PLGA having a first specific viscosity between about 0.01 and about 0.31 dL/g with PLGA having a second specific viscosity between about 0.40 and 0.88 dL/g as recited in claim 1; the pharmaceutical formulation made admixing PLGA having a first specific viscosity between about 0.01 and about 0.31 dL/g with PLGA having a second specific viscosity between about 0.40 and 0.88 dL/g as recited in claim 17; or the method of treatment of the claimed microspheres recited in claim 20.

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America's oldest commercial source of biodegradable polymers

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Standard Products

DURECT offers the following standard products:

Product Number	Chemical Name	Common Name	Inherent Viscosity
50DG020*	50/50 Poly (DL-lactide-co-glycolide)	50:50 DLPLG	0.15 - 0.25
50DG040*	50/50 Poly (DL-lactide-co-glycolide)	50:50 DLPLG	0.26 - 0.54
50DG065*	50/50 Poly (DL-lactide-co-glycolide)	50:50 DLPLG	0.55 - 0.75
50DG085*	50/50 Poly (DL-lactide-co-glycolide)	50:50 DLPLG	0.76 - 0.94
50DG105*	50/50 Poly (DL-lactide-co-glycolide)	50:50 DLPLG	0.95 - 1.20
65DG065*	65/35 Poly (DL-lactide-co-glycolide)	65:35 DLPLG	0.55 - 0.75
75DG065	75/25 Poly (DL-lactide-co-glycolide)	75:25 DLPLG	0.55 - 0.75
85DG065	85/15 Poly (DL-lactide-co-glycolide)	85:15 DLPLG	0.55 - 0.75
100D020A	Poly (DL-lactide-COOH)	DLPLA-COOH	0.15 - 0.25
100D040A	Poly (DL-lactide-COOH)	DLPLA-COOH	0.26 - 0.54
50DG020A	50/50 Poly (DL-lactide-co-glycolide)-COOH	50:50 DLPLG-COOH	0.15 - 0.25
50DG065A	50/50 Poly (DL-lactide-co-glycolide)-COOH	50:50 DLPLG-COOH	0.55 - 0.75
100D040	Poly (DL-lactide)	DLPLA	0.26 - 0.54
100D065	Poly (DL-lactide)	DLPLA	0.55 - 0.75
100L105	Poly (L-lactide)	LPLA	0.90 - 1.20
100C115	Poly (e-caprolactone)	PCL	1.00 - 1.30
25DC080**	25/75 Poly (DL-lactide-co-e-caprolactone)	25:75 DLPLCL	0.70 - 0.90
80DC080**	80/20 Poly (DL-lactide-co-e-caprolactone)	80:20 DLPLCL	0.70 - 0.90

*Inherent viscosity of 50:50 DLPLG and 65:35 DLPLG measured in hexafluoroisopropanol. The inherent viscosity of other polymers measured in chloroform.

**Not currently in stock. Please call for quote and availability.

Sample Kits are also available.

Standard Products

Custom Synthesis

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New!

Inherent Viscosity vs. Molecular Weight Chart for Selected Polymers

50/50 DLPLG
65/35 DLPLG
75/25 DLPLG
85/15 DLPLG
DLPLA

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Custom Synthesis

For many customers, we prepare custom polymers with specific characteristics, such as molecular weight and copolymer ratio. We also tailor end groups of polymers, most commonly either acid or ester group, because a subtle change in molecular architecture can have a profound effect on water uptake, degradation rate and drug delivery.

We have recently worked with clients to:

- increase polymer solubility
- increase molecular weight for enhanced mechanical properties
- tightly control low-molecular-weight polymers that degrade rapidly
- change molar ratios to give desired drug-release profiles

We work closely with our clients through the entire FDA approval process. Often, our custom synthesis capabilities help us anticipate validation questions for new production processes. For example, we can supply three reproducible lots to validate a process. Or we can target molecular weights 10% above and below your mean to aid in setting raw material specifications.

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WEB DEVELOPMENT BY INFOMEDIA

EXHIBIT C

LACTEL.
Absorbable Polymers

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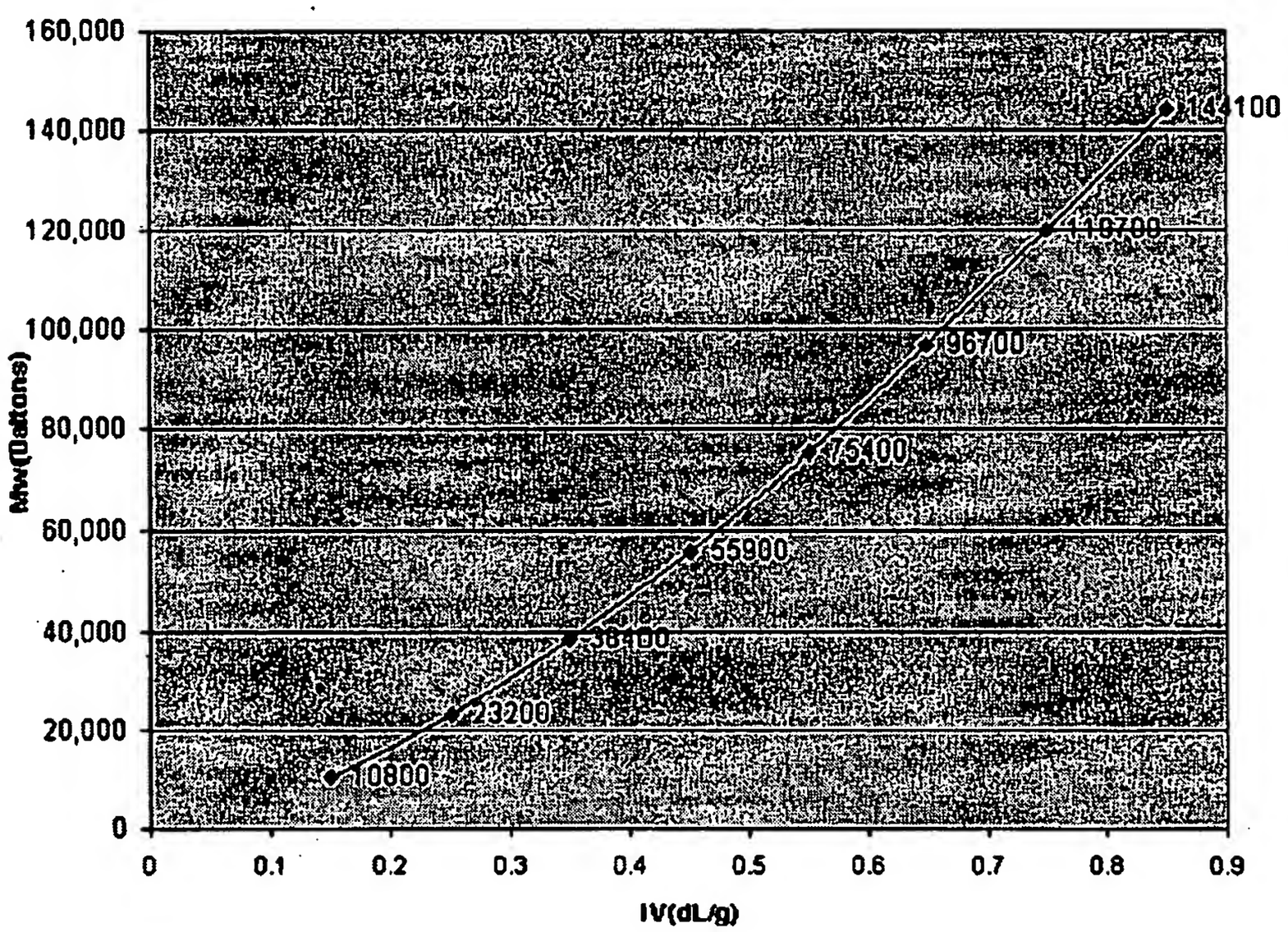
50/50 DLPLG



LACTEL. Absorbable Polymers

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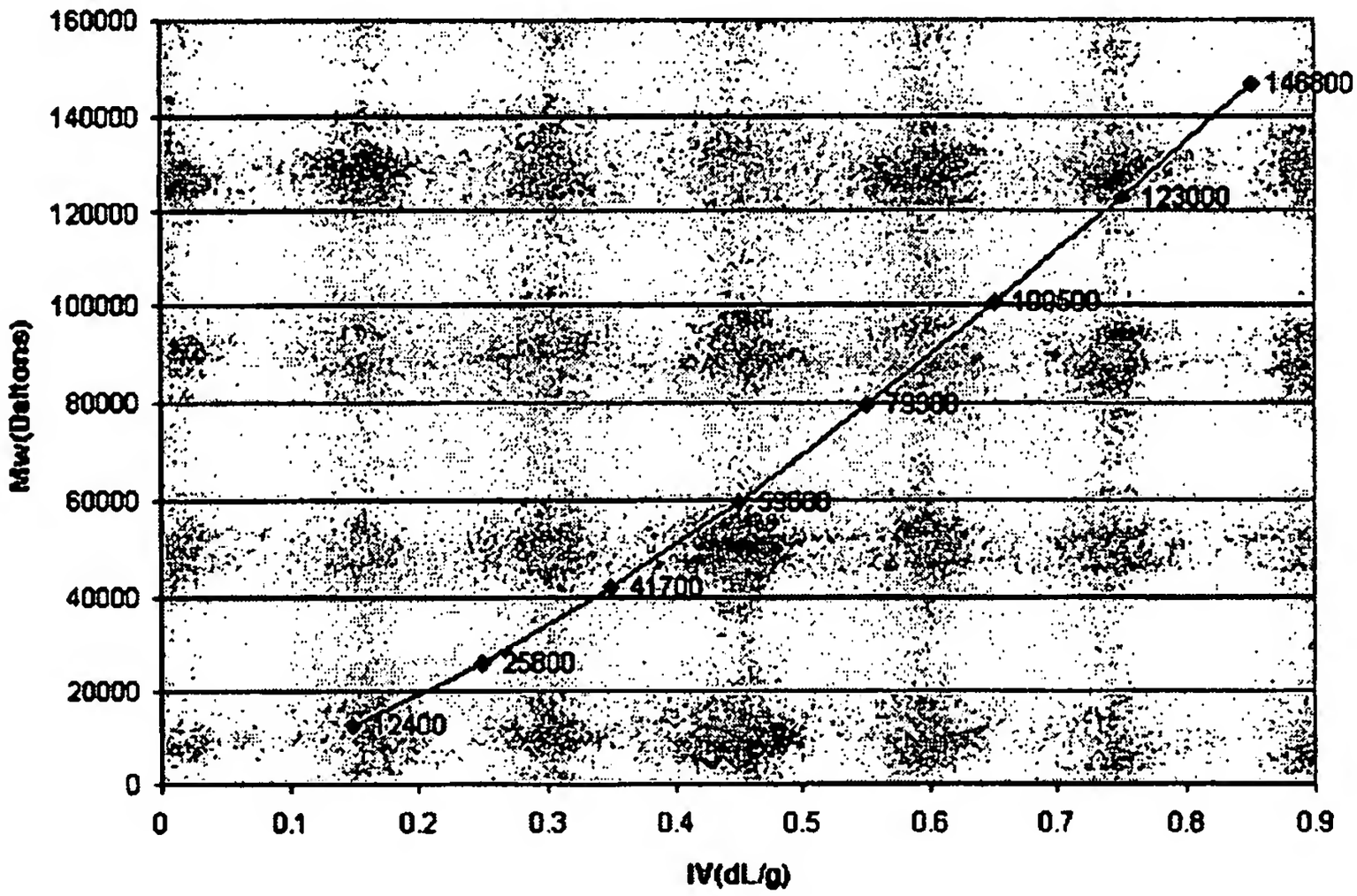
65/35 DLPLG



LACTEL.
Absorbable Polymers

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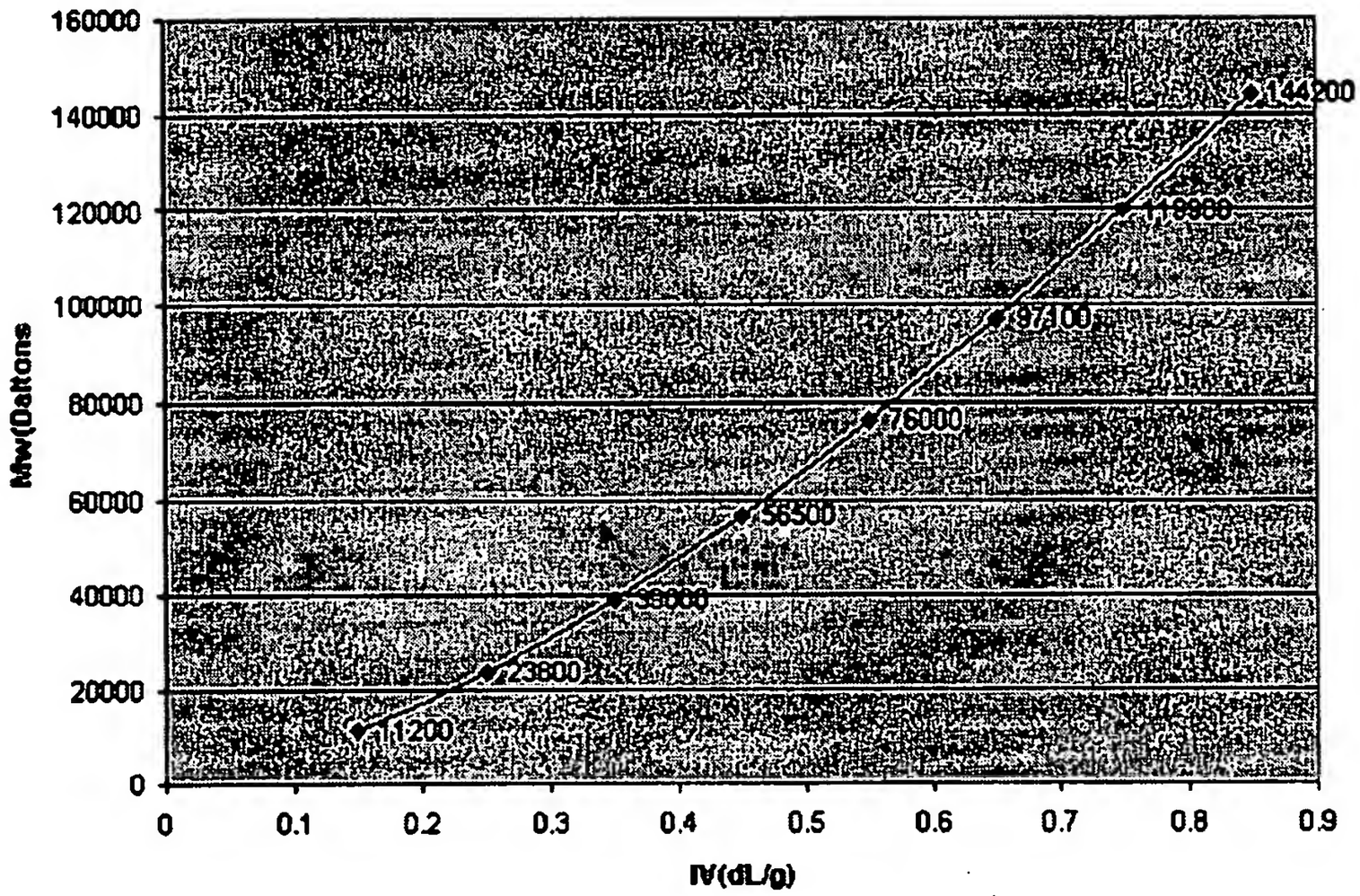
75/25 DLPLG



LACTEL Absorbable Polymers

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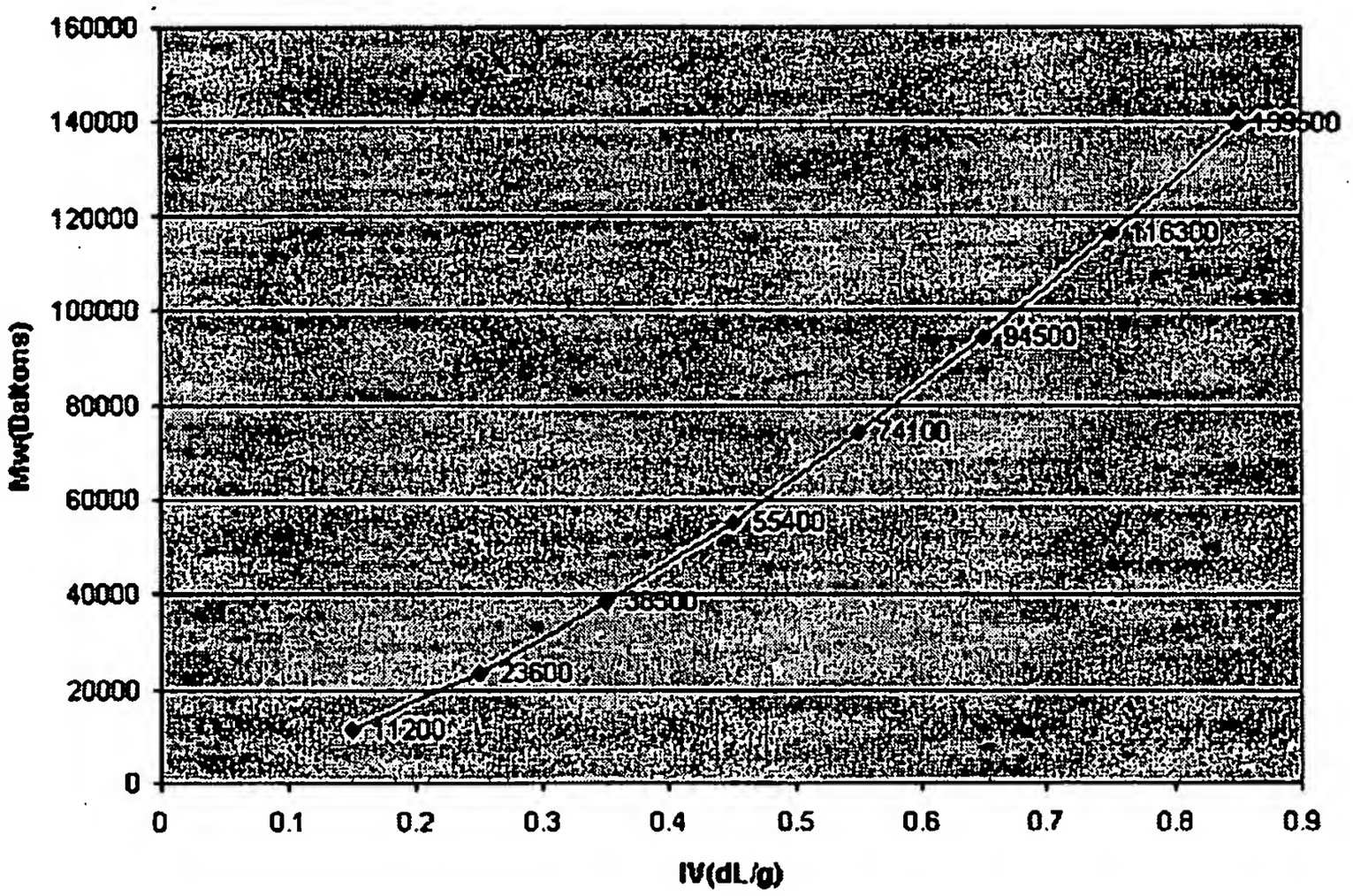
85/15 DLPLG



LACTEL.
Absorbable Polymers

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DLPLA

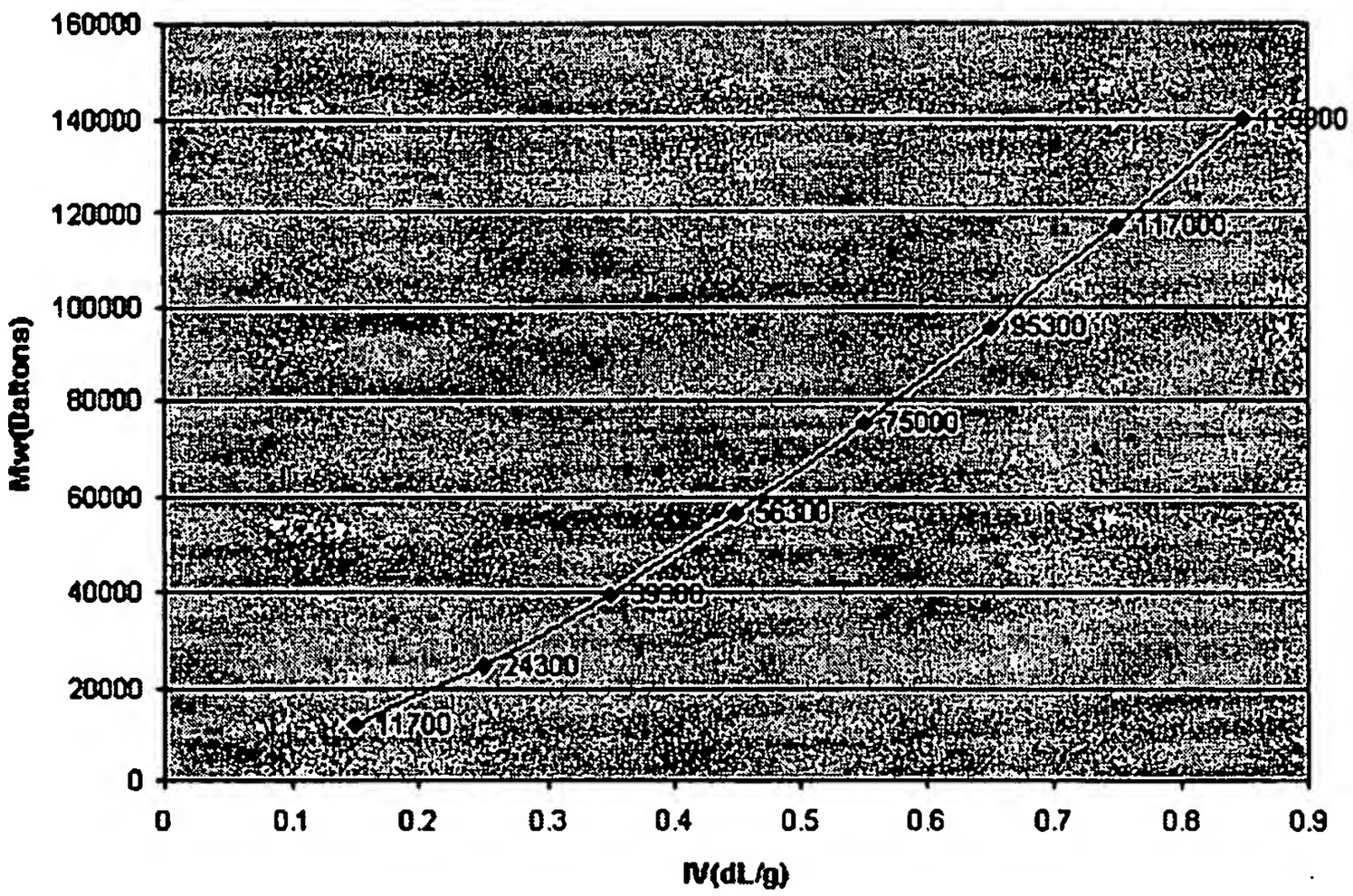

EXHIBIT D

LACTEL. Absorbable Polymers

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Products and Services

Current Applications

The most active area of research using biodegradable polymers is in controlled delivery of pharmaceuticals. In the last decade, this research has led to the commercial development of numerous drug delivery systems in Europe, Japan, and the United States. The two most common commercial delivery systems using biodegradable polymers are microspheres (Lupron Depot®) and implants (Zoladex®). The implants can be rods, films, or other shapes depending upon the specific needs. Recently, gel-based systems using biodegradable polymers have been introduced, further expanding delivery system options.

These delivery systems are also being considered for the treatment of cancer, viral and bacterial infections, birth control, chemical dependency, AIDS, and chronic pain.

Medical Devices

Biodegradable polymers of lactide, glycolide, and e-caprolactone are currently being used to produce a variety of commercial medical devices. These include:

- Biodegradable sutures - product names include Dexon®, Maxon®, Polysorb®, and BiosynTM, among others
- Interference screws - including Bioscrew®, Sysorb®, Endofix® and more
- Pins and rods - product names include Biofix®, and Resor-Pin®
- Other products - Bio-Anchor® (Suture Anchor), Drilac® (Dental), LactoSorb® (plate, mesh, screws), and more.

In addition to biocompatibility and non-toxicity, other properties that make these polymers uniquely suited for medical devices include thermoplasticity, strength, controlled crystallinity, degradation, and hydrophilicity. Because of these same properties, these polymers are also being considered for bone plates and other orthopedic applications, ear vent tubes, nerve growth tubes, stent coatings, and wound dressings.

The Near Future

Many new controlled drug delivery products are expected to emerge in the near future, as a result of the extensive research and

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development efforts currently underway. Because polymers and copolymers of glycolide, lactide, and e-caprolactone have a proven record of success, it is expected that they will be the dominant excipients used in most formulations.

Our Expertise

At DURECT Corporation, we can synthesize and manufacture polymers to meet your specific needs. We know that choosing a polymer for your particular application depends upon a number of requirements - including mechanical properties, degradation rate, and processing. There might be a standard polymer that meets your exact specifications, and we can help you select that polymer. However if additional product optimization is required, we provide experimental input and custom synthesis. For example, increased polymer solubility aids in the preparation of many microsphere products. To meet our customers' needs in this area, we have used our synthetic expertise to increase polymer solubility of 50/50 poly (DL-lactide-co-glycolide). We have also used end group chemistry, such as free carboxylic acids and PEG to effect degradation and tailor release kinetics.

Synthesis

All polymer production is in accordance with applicable current Good Manufacturing Practices (cGMP) of the FDA. Polymers are produced in class 100,000 clean rooms with controlled temperature and humidity in our modern, well-equipped production and laboratory facilities in Pelham, Alabama, USA. Large-scale processes are tightly controlled to maintain consistent processing parameters and to automatically log all data for quality assurance record retention. Both Drug and Device Master Files are maintained with the FDA.

Our commitment to quality includes a thorough analysis of each lot of polymer. Polymer lots are tested before shipment, and each lot is supplied with a Certificate of Analysis (COA). Our basic analyses include identification by FTIR or 1H-NMR, inherent viscosity (IV), monomer ratio by 1H-NMR (copolymers only), residual Sn+2 (from catalyst), bioburden (total aerobes, anerobes and spores), and pyrogens (LAL). Other analyses can be provided if desired, including other metals and molecular weight by GPC.

LACTEL Customer Service
Phone: 877-705-8072
Fax: 408-865-1406
E-mail:absorbablescs@durect.com

LACTEL Technical Support
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